# PROFILE OF BLADDER TRANSITIONAL CELL CANCER IN SOETOMO HOSPITAL SURABAYA

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***ABSTRACT***

***Objectives:*** *To describe the characteristic of bladder transitional cell cancer (TCC).* ***Material & methods:*** *We reviewed the medical records of patients with bladder TCC admitted in Soetomo General Hospital Surabaya, from January 2008 until December 2012. The data regarding demographic characteristics, clinical presentation and staging, grading and staging based on pathological examinations results, and the management of the cancer.* ***Results:*** *The 126 cases, consisted of 102 men (81%) and 24 women (19%) with its ratio was 4.2 : 1. All male patients were heavy cigarette smokers. Mean age was 57.8 years, peak incidence was 50-59 years. Hematuria was the most frequent clinical presentation (112 patients, 88.9%), urinary retention and other complaints (12 patients, 9.5%), and chronic dysuria (2 patients, 1.6%). Clinical staging was T1 as NMIBC in 7 patients (5.7%). MIBC consisted of T2 in 37 patients (30.3%), T3 in 35 patients (28.7%), T4 in 43 patients (35.2%). The pathological grading as an high-grade were 74 patients (64.3%). All patients had underwent TURBT for diagnosis and staging, followed by definitive treatment. It consisted of TURBT and chemotherapy bladder instillation in 7 patients (5.6%), radical cystectomy in 13 patients (10.3%), EBRT in 5 patients (4%), MVAC chemotherapy in 24 patients (19%), EBRT and chemotherapy with MVAC in 3 patients (2.4%). There were 74 patients (58.7%) underwent TURBT alone.* ***Conclusion:*** *Bladder TCC was in advanced stage when diagnosed, most of the patients received only TURBT and refused further treatment.*

***Keywords:*** *Bladder transitional cell cancer, characteristics, managements.*

***ABSTRAK***

***Tujuan:*** *Menggambarkan karakteristik kanker buli.* ***Bahan & cara:*** *Kami secara retrospektif meninjau rekam medis pasien dengan sel kanker buli yang masuk di RSUD Dr. Soetomo Surabaya antara Januari 2008 sampai Desember 2012. Data tersebut meliputi karakteristik demografi, presentasi klinis, dan staging saat didiagnosa, grading dan staging berdasarkan pemeriksaan patologi, dan juga manajemen kanker.* ***Hasil:*** *Dari total 126 kasus, terdiri dari 102 laki-laki (81%) dan 24 wanita (19%), dengan rasio laki-laki dan wanita 4.2 : 1. Semua pasien laki-laki adalah perokok berat. Rerata umur adalah 57.8 tahun dengan puncak insiden ditemukan pada umur 50-59 tahun. Hematuria adalah sebagian besar presentasi klinis umum (112 pasien, 88.9%), diikuti retensi urine dan keluhan lain (12 pasien, 9.5%), dan disuria kronis (2 pasien, 1.6%). Staging klinis pasien saat didiagnosa adalah 7 pasien (5.7%) pada T1 sebagai NMIBC. MIBC terdiri dari T2 pada 37 pasien (30.3%), T3 pada 35 pasien (28.7%), dan T4 pada 43 pasien (35.2%). Grading patologi pada grade tinggi 74 pasien (64.3%). Semua pasien telah menjalani TURBT untuk diagnosa dan staging, diikuti oleh perawatan definitif. Perawatan definitif terdiri dari TURBT dan kemoterapi instilasi kandung kemih pada 7 pasien (5.6%), radikal sistektomi pada 13 pasien (10.3%), EBRT pada 5 pasien (4%), kemoterapi dengan MVAC pada 24 pasien (19%), EBRT dan kemoterapi dengan MVAC pada 3 pasien (2.4%). Terdapat 74 pasien (58.7%) yang hanya menjalani TURBT.* ***Simpulan:*** *Kanker buli dalam stase awal saat didiagnosa dan sebagian besar pasien menerima hanya TURBT dan menolak perawatan lebih lanjut.*

***Kata kunci:*** *Kanker buli, karakteristik, manajemen.*

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## INTRODUCTION

The incidence of carcinoma of the bladder (CaB) in men is 10.1 per 100.000 population while its incidence in women is 2.5.[1] Based on Globocan Data, 2008, the incidence of CaB patients in Indonesia for men and women per 100.000 population were 4.9-10.6 and 1.2-1.8, respectively.[2]

Risk for CaB is doubled for people who have family history of CaB. The risk factors for CaB are cigarrete smoking, exposure to carcinogens, nutritional factors, environmental pollution, socioeconomic status, race, gender, and certain medical conditions such as diabetes mellitus and schistosomiasis.[3] Cigarette smoking is a major risk factor for the occurrence of the CaB. The incidence of CaB four times lower in women, while mortality is higher than men.[3,4]

CaB can be staged according to clinical parameters of tumor, node, and metastasis (TNM).5 For purpose of treatment options, it can also be classified as non-muscle invasive bladder cancer (NMIBC) and muscle-invasive (MIBC). According to cellular differentiation, CaB can be classified into urothelial papilloma, grade 1 (well differentiated), grade 2 (moderately differentiated), and grade 3 (poorly differentiated).[6]

A classic symptom for CaB is gross hematuria (occult), painless, and intermittent. This triad of hematuria is found in 80% of CaB patients. Approximately 10% of complaints are caused by the process of metastasis. Dysuria and other irritative complaints are found in approximately 30% of CaB patients.[7] Imaging examination for detection of CaB include intravenous pyelography (IVP), ultrasound, and Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI).[6-9] The sensitivity of urine cytology is very varied ranging from 28-100%, which is quite sensitive to high-grade tumors and CIS and often give negative results on the low-grade of tumors.[7,10-12] BTA stat, NMP22, ucyt +/immunoCyt, UroVysion FISH, and microsatellite analysis are some of the tumor markers for CaB that has been studied and researched. Sensitivity and specificity of that five markers for the detection of CaB are still too low when compared with cystoscopy as the gold standard.[10-12] Combined with urine cytology and pathology examination results, cystoscopy is the gold standard for diagnosis of CaB, CIS, and others bladder tumors.[6,8,9,13]

Therapeutic modalities for CaB may be TURBT (Transurethral Resection of Bladder Tumor), radical cystectomy, local or systemic chemotherapy, radiotherapy, or combination of these. The choice of therapy is determined by tumor staging and pathology, as well as the condition of the individual patient (fit or unfit).6 For NMIBC, TURBT followed by intravesical instillation of cytostatic is a main strategy.[14] Radical cystectomy with or without adjuvant therapy provide a good survival rate and low local recurrence for organ confined or nonorgan-confined MIBC with negativenodes.[14-17] For locally advanced or metastatic CaB, cisplatin-based combination chemotherapy or gemcitabine/cisplatin provide long-term survival and reduce progression rate. Its lower toxicity making gemcitabine/cisplatin as a new standard chemotherapy regimen and replacing a classic MVAC (Methotrexate, Vinblastine, Adriamycin, Cisplatin) regimen.[16,18,19]

Radiotherapy is an alternative to the radical cystectomy, especially for older patients and whom with high-risk (unfit) for the complications of operation.[16,20] The addition of chemotherapy fluorouracil and mitomycin C versus standard-dose radiotherapy is associated with decreased locoregional recurrence rate with no significant toxicity.[20]

## OBJECTIVE

To describe the characteristic of patients with bladder transitional cell cancer (TCC) who admitted in Soetomo General Hospital Surabaya, from January 2008 until December 2012.

## MATERIAL & METHOD

This is a retrospective and descriptive study design. The entire medical records of patients with CaB hospitalized in The Department of Urology Soetomo General Hospital Surabaya, between January 2008 and December 2012 were collected and analyzed. Variables collected were demographic aspects including number of patients, age, gender, ratio of men to women, risk factors of smoking; diagnostic aspects include chief of complaint, urine cytology and tumor markers, clinical staging, tumor grading and pathology examination results, as well as the therapeutic aspects. The collected data were analyzed to determine overall number of CaB, ratio between men and women patients, age characteristics, percentage of heavy smokers (more than 2 packsper day), patient chief complaints, stage, and grading of histopathology results, as well as treatment performed. All analysis results are displayed in tables and described narratively.

## RESULTS

During the period of January 2008 until December 2012, there were 126 patients with CaB

hospitalized in the Department of Urology Soetomo General Hospital Surabaya. They consisted of 102 men (80.9%) and 24 women (19.1%). The ratio of men to women was 4.2 : 1. The average age of patients was 57.8 years. The age of majority was in the range of 50-59 years. All patients had a history of smoking in men, whereas no women smoked. When compared with all CaB patients, smoking history was present in 80.2% of cases.

The chief of complaint for the majority of the patients is gross, painless, intermittent hematuria (112 patients, 88.9%), urinary retention or other complaints (12 patients, 9.5%), and chronic dysuria (2 patients, 1.6%). Urine cytology was performed in 102 patients (81%) showing negative results or no malignant cells (78 patients; 76.5%), atypical cells (14 patients; 13.5%) and malignant cells (10 patients; 9.8%). The examination of tumor markers was only done in 2 patients (1.5%).

**Table 1.** Chief complaints.

| Chief complaints | Number | Percentage |
|---|---|---|
| Gross, painless, intermitten hematuria | 112 | 88.9 |
| Chronic dysuria | 2 | 1.6 |
| Urinary retention and others | 12 | 9.5 |

**Table 2.** Urine cytology results.

| Class | Number | Percentage |
|---|---|---|
| 1 (normal/negative) | 78 | 76.5 |
| 2 (inflammatory cells) | 0 | 0 |
| 3 (atypical) | 14 | 13.7 |
| 4 (suggested malignant cells) | 0 | 0 |
| 5 (malignant cells) | 10 | 9.8 |

The majority of CaB patients was in advanced stage, above T2 when diagnosed (115 patients, 91.3%). The details are T2 in 37 patients (30.3%), T3 in 35 patients (28.7%), and T4 in 43 patients (35.3%). The early stage (T1) and classified as NMIBC is 7 patients (5.7%). There are 4 patients (3.6% of all samples) were no data in the medical record

**Table 3.** Stage of tumor.

| Stage | Number | Percentage |
|---|---|---|
| T1 | 7 | 5.7 |
| T2 | 37 | 30.3 |
| T3 | 35 | 28.7 |
| T4 | 43 | 35.3 |
| No data | 4 | 3.6 |

Based on histopathology grading, 74 patients have poorly differentiated tumors (high-grade; 64.3%), 16 patients with moderate differentiation (moderate-grade, 14%), and 25 patients with well-differentiated (low-grade, 21.7%). There were 11 patients (8.7% of all samples) not recorded in the medical record. According to muscle invasion, 108 patients (85.7%) showed a pathology result as muscle-invasive while 8 patients (6.3%) had no evidence of muscle invasion. Ten patients (8% of all samples) had no data recorded.

**Table 4.** Histopathology grading.

| Grade | Number | Percentage |
|---|---|---|
| High grade | 74 | 64.3 |
| Moderate grade | 16 | 14 |
| Low grade | 25 | 21.7 |
| No data | 11 | 8.8 |

**Table 5.** Invasion to muscle.

| Invasion to muscle | Number | Percentage |
|---|---|---|
| Yes | 108 | 85.7 |
| No | 8 | 6.3 |
| No data | 10 | 8 |

In the aspect of therapy, all patients underwent TURBT procedure to confirm the diagnosis and stage, as well as to determine the next definitive treatment options. The definitive therapy consisting of TURBT followed by intravesical instillation of cytostatic agents, radical cystectomy, radiotherapy, chemotherapy, and chemoradio-therapy. There are 7 patients (5.6%) who underwent intravesical instillations. Radical cystectomy performed in 13 patients (10.3%), radiotherapy in 5 patients (4%), systemic chemotherapy with MVAC regimen in 24 patients (19%), and combination of radiotherapy and MVAC chemotherapy in 3 patients (2.4%). There are 73 patients (57.9%) who only underwent TURBT procedure as palliative therapy without any other definitive therapy followed.

**Table 6.** Therapy.

| Therapy | Number | Percentage |
|---|---|---|
| TURBT + intravesical cytostatic instillation | 7 | 5.6 |
| Radical cystectomy | 13 | 10.3 |
| Radiotherapy | 5 | 4 |
| MVAC chemotherapy | 24 | 19 |
| MVAC chemotherapy and radiotherapy | 3 | 2.4 |
| TURBT only | 74 | 58.7 |

**Table 7.** Profile of CaB patients.

| Variables | Total | Percentage (%) | Comments |
|---|---|---|---|
| Total patients | 126 | | |
| Men; Women | 102; 24 | 81; 19 | |
| Ratio men : women | 4.2 : 1 | | |
| Mean age; Mode of Age Group | | | 57.8 yo; 50-59 yo |
| Smoking history | | | |
| Men; Women | 102; 0 | 81; 0 | |
| Chief complaint | | | |
| Gross, painless, intermittent hematuria | 112 | 88.9 | |
| Chronic dysuria | 2 | 1.6 | |
| Urinary retention and others | 12 | 9.5 | |
| Clinical staging | | | 4 patients (3.2%) |
| T1; T2 | 7; 37 | 5.7; 30.3 | no data |
| T3; T4 | 35; 43 | 28.7; 35.3 | |
| Histopathology grading | | | 11 patients (8.7%) |
| High grade | 74 | 64.3 | no data |
| Moderate grade | 16 | 13.9 | |
| Low grade | 25 | 21.7 | |
| Invasion to muscle | | | 10 patients (7.9%) |
| Yes; No | 108; 8 | 85.7; 6.3 | no data |
| Definitive treatment | | | |
| TURBT + intravesical cytostatic instillation | 7 | 5.6 | |
| Radical cystectomy | 13 | 10.3 | |
| Radiotherapy | 5 | 4 | |
| MVAC Chemotherapy | 24 | 19 | |
| Radiotherapy and MVAC chemotherapy | 3 | 2.4 | |
| TURBT only | 74 | 58.7 | |

Table 7 shows the profile of CaB patients in the Department of Urology Soetomo General Hospital Surabaya period January 2008 until December 2012.

## DISCUSSION

Based on the results obtained, the ratio of men to women with CaB was 4.2 : 1. This result is not much different from Ploeg et al. They mentioned that risk of developing CaB for men is 1 in 25, while for women is 1 in 80. This means the ratio of men to women to be exposed to the CaB is 3.2 : 1.[1] In Europe, it was reported that the incidence of CaB for men is 27 per 100.000 population, while for women is 6 per 100.000 population. In general, the worldwide incidence of CaB in men is 9 per 100.000 population and in women is 2 per 100.000 population, which means the men to women ratio is 4.5 : 1.[6]

Smoking is a major risk factor and is strongly correlated with the CaB. Based on the results obtained, all men with CaB were heavy smokers (more than 2 packs per day) whereas in all

women patients had no smoking history. Compared to all CaB patients, smoking history was found in 81% of the cases. Burger et al states that the risk ofCaB for men smokers was 50-60% and for women smokers was 20-30%.[3] Compared to non-smokers, the risk of those who have a history of smoking (former smoker) and current smokers to get CaB is 2.22 and 4.06 times higher.[3] There were not any history of smoking for all women patients in this study. This can be explained that the occurrence of CaB in those patients may be due to predominantly other risk factors such a genetic factor or exposure to cigarette smoke (passive smoker).

Based on the results obtained, gross, painless, and intermittent hematuria as a chief complaint is most commonly found in CaB patients (88.9%), followed by urinary retention and chronic dysuria (9.5% and 1.6%). Siroky et al, states that the classic symptoms of a CaB that is gross (occult), painless (no pain), and intermittent hematuria exist in 80% of CaB patients.[7] Approximately 10% of complaints are caused by the process of metastasis. Dysuria and other irritating complaints found in approximately 30% of CaB patients.[7]

Urine cytology performed on 102 patients (81%), the remainder (19%) are not documented in the medical record. Examination of tumor marker has not become a routine protocol in The Department of Urology Soetomo General Hospital Surabaya. NMP22 examination in 2 patients (1.5%) was performed as part of other studies on the diagnostic value for detection of CaB.

Based on the results obtained, CaB patients was in the advanced stage when diagnosed (above T2 in 115 patients, 94.3%). In detail, T2 in 37 patients (30.3%), T3 in 35 patients (28.7%), and T4 in 43 patients (35.2%). While 7 patients (5.7%) diagnosed at an early stage (T1) and classified as NMIBC is. There were 4 patients (3.2%) not recorded in the medical record of the tumor stage. These are consistent with the results of histopathology grading examination and description of tumor invasion into the muscle. The pathology examination of tumor tissue resected from TURBT procedure showed 74 patients in poorly differentiated (high-grade, 64.3%), 16 patients in moderately differentiated (moderate-grade, 13.9%), and 25 patients with well-differentiated (low-grade, 21.7%). There were 11 patients (8.7%) with no data recorded about their pathology grading. According to the invasion of muscle, 108 patients (85.7%) showed a muscle-invasive bladder cancer whereas 8 patients (6.3%) had not. Ten patients (7.9%) were no data about their muscle invasion.

Based on the data above, the results of clinical staging and histopathology grading showed a significant differences with the literature. Burger, Babjuk, Stenzl, et al, states that approximately 75% of newly diagnosed cases of CAB is in the non-invasive stage. The remaining (25%) are cases of CaB newly diagnosed in advaced stage (muscle-invasive).[3,6,16] Such differences may be caused by the high awareness of the health, access to better health services, early detection rates in European countries and America compared to emerging countries such in Indonesia.

All CaB patients underwentTURBT procedure to confirm the diagnosis and staging, as well as to determine the next definitive treatment options. TURBT procedure is the main protocols and mandatory to performed in The Department of Urology Soetomo General Hospital Surabaya for patients who are clinically diagnosed CaB. The definitive therapy consisting of TURBT followed by intravesical instillation of cytostatics, radical cystectomy, radiotherapy, chemotherapy, and chemoradiotherapy. There were 7 patients (5.6%) who underwent intravesical instillation of cytostatics. In contrast to the literature or other international guidelines using Mitomycin C,6,8,9,16 intravesical chemotherapy used in The Department of Urology Soetomo General Hospital is Epirubic in due to availability in social health insurance medication list (Jamkesmas, People Health Insurance).

Radical cystectomy was performed in 13 patients (10.3%), on average 3 procedures of cystectomy with Bricker's urinary diversion or neobladder was performed annually. Radiotherapy is performed in 5 patients (4%), the combination of radiotherapy and MVAC chemotherapy is in 3 patients (2.4%). Radiotherapy as definitive therapy for patients with locally advanced CaB (T3 and T4) who are unfitor refused radical operation seems suitable. Because of limited facilities resulting in 6 months queue for radiotherapy, patients were also offered systemic chemotherapy.

According to T-stage and histopathology grading, actually most of the patients need a radical treatment such as radical cystectomy or curative external radiotherapy but in fact many patients refused that treatment option.

Systemic chemotherapy is performed in 24 patients (19%). Chemotherapy regimens used are

classic MVAC regimens. Based on the literature and other international guidelines,[16,18,19] because of low toxicity, gemcitabine/cisplatin is becoming a new standard in CaB chemotherapy regimens. This can not be applied to the patients treated in The Department of Urology Soetomo General Hospital Surabaya. The reason is the high cost of the regimens and are not covered by health insurance (Jamkesmas), as well as the availability of preparations of gemcitabine in the hospital. Meanwhile, there were 74 patients (58.7%) who only underwent TURBT procedure. This is the most frequent treatment that performed to the CaB patients. Refusal of further treatment by the patients, palliative treatment, loss of control, died, or not recorded in the medical record are several reasons that can be explained for the patients who underwent only TURBT without any others definitive treatments.

## CONCLUSION

Based on this study, we conclude that the characteristics and management of bladder cancer in Urology Department Soetomo General Hospital Surabaya were in advanced stage when diagnosed and most of the patients received only TURBT and refused any further definitive treatments.

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